REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Applicants have not received an initialed copy of the PTO 1449 form (citing 63 references) that accompanied the Information Disclosure Statement mailed on May 7, 2003 (copy enclosed). It is respectfully requested that these references be considered, that the enclosed PTO-1449 form be initialed to reflect such consideration, and that the initialed PTO 1449 form be returned with the next office action.

By the above amendments, new claims 35-38 have been added. Support for these claims is found in the specification as filed on page 13, lines 17-28. Thus, no new matter has been entered.

The rejection of claims 1-34 under 35 U.S.C. § 112 (2nd paragraph) as being incomplete for omitting essential steps is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the claims omit the essential steps of "using a thin skull, using the particular wavelength required for multiphoton excitation, using the required power level and pulsed durations and the summing of the low energy photons." Applicants respectfully disagree.

The claims of the present application are complete and recite all steps which are necessary for the claimed method to function.

Specifically, claim 1 is directed to a method of detecting a neurodegenerative disease in a mammal. This method involves activating brain tissue of the mammal by application of radiation under conditions effective to promote a simultaneous multiphoton excitation of the brain tissue and to emit a fluorescence characteristic. The fluorescence characteristic is compared to a standard fluorescence emitted by exciting healthy brain tissue of the mammal under the same conditions used to carry out the activating. Brain tissue where the fluorescence characteristic differs from the standard fluorescence is identified as having a neurodegenerative disease.

Claim 19 of the present invention is directed to a method of producing an image of brain tissue from a mammal. This method involves activating brain tissue of a mammal with radiation applied under conditions effective to promote a simultaneous multiphoton excitation of the brain tissue and to produce a fluorescence. The fluorescence is collected to produce an image of the brain tissue.

By the above rejection, the PTO is essentially requiring that the present claims be limited to preferred embodiments taught in the specification. Yet, it is well-known that a claim need not be so limited. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) ("It is a truism that a claim need not be limited to a preferred embodiment."); *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc) ("If everything in the specification were required to be read into the claims, or if structural claims were to be limited to devices operated precisely as a specification-described embodiment is operated, there would be no need for claims. Nor could an applicant, regardless of the prior art, claim more broadly than that embodiment. Nor would a basis remain for the statutory necessity that an applicant conclude his specification with 'claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.'" (citing 35 U.S.C. § 112")); *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1348 (Fed. Cir. 2000) (Newman, J. concurring) ("Section 112 P2 instructs the applicant to 'distinctly claim[] the subject matter which the applicant regards as his invention.' This does not automatically require inclusion in every claim of every element that is part of the device or its operation. . . .When the claim is supported by the patent's disclosure, is adequately distinguished from the prior art, and otherwise meets the statutory requirements of patentability, neither law nor policy requires that the claim contain all the elements described in the specification as part of the . . .method.").

The requirement under 35 U.S.C. § 112 (2nd paragraph) that the claims particularly point out and distinctly claim the invention merely requires that the claims be clear to a person of ordinary skill in the art. *Orthokinetics, Inc. v. Safety Travel*, 806 F.2d 1565, 1576 (Fed. Cir. 1986) ("A decision on whether a claim is invalid under § 112, 2d para., requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."). The claimed methods of detecting a neurodegenerative disease in a mammal and producing an image of brain tissue from a mammal are clear. In fact, the PTO has made no assertion in the outstanding office action that the claims would not be understood by a person of ordinary skill in the art.

Accordingly, the rejection of claims 1-34 under 35 U.S.C. § 112 (2nd paragraph) should be withdrawn.

The rejection of claims 1-34 under 35 U.S.C. § 101 for lack of utility is respectfully traversed.

Compliance with 35 U.S.C. § 101 requires that the written description provide a credible assertion of specific and substantial utility of the claimed invention. *Brenner v. Manson,* 383 U.S. 519 (1966). As stated throughout the specification, the present invention is directed to detecting a neurodegenerative disease and imaging brain tissue using multiphoton excitation. Given the success of the experiments carried out in the Examples, one of ordinary skill in the art would find the usefulness of the present invention credible.

Therefore, the rejection of claims 1-34 under 35 U.S.C. § 101 for lack of utility should be withdrawn.

The rejection of claims 1-34 under 35 U.S.C. § 112 (1st paragraph) for lack of enablement is respectfully traversed.

The specification fully enables a person of skill in the art to practice the claimed methods without undue experimentation. In particular, conditions effective to promote a simultaneous multiphoton excitation of brain tissue by application of radiation may be carried out, according to one preferred embodiment, by thinning (e.g., drilling or abrading) the mammal's skull (page 11, lines 5-6) or, in an alternative embodiment, by performing a craniotomy (page 11, lines 6-7). Suitable wavelengths by which activation of brain tissue is carried out are also specifically taught as are various preferred power levels and pulse durations (page 13, line 17 to page 15, line 5). Preferred embodiments of how low energy photons are to be summed are also specifically taught by the present application (page 12, line 24 to page 13, line 16).

The enablement requirement of 35 U.S.C. § 112 (1st paragraph) is satisfied by what is disclosed in the specification and not by what is found in the claims:

> That claims are interpreted in light of the specification does not mean that everything expressed in the specification must be read into all the claims. On the contrary, as was said in *Environmental Designs, supra,* 713 F.2d [693,]...699, 218 *USPQ* [865,]...871 [(Fed. Cir. 1983)]:
>
> > the specification must be sufficiently explicit and complete to enable one skilled in the art to practice the invention, while a claim defines only that which the patentee regards as his invention. *35 U.S.C. § 112.* The claim, not the specification, measures the invention. (Case cited). The argument that claim 1 must include a limitation found in the specification is thus legally unsound. *Smith v. Snow* 294 U.S. 1, 79 L. Ed. 721, 55 S. Ct. 279 (1935).

Raytheon Co. v. Roper Corp. 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983). In view of the subject matter disclosed in the specification of the present application, it is clear that the present application is enabling.

A rejection under 35 U.S.C. § 112 (1st paragraph) for lack of enablement on the grounds that a critical limitation is absent from the claims is only proper when the specification clearly states that the limitation is a critical feature of the invention:

> Limiting an applicant to the preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting the progress in the useful arts. Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.

MPEP § 2164.08(c). The disclosure in the specification clearly satisfies this standard by generally describing the present invention and identifying a number of alternative embodiments for carrying out the claimed methods. Therefore, the claims need not be limited to these embodiments.

Since the present application fully enables the claimed invention, the rejection of claims 1-34 under 35 U.S.C. § 112 (1st paragraph) should be withdrawn.

The rejection of claims 1-34 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent Publication No. 2002/0115717 to Gervais et al., ("Gervais") in view of U.S. Patent No. 6,280,386 to Alfano et al. ("Alfano") and Christie et al., "Multiphoton Imaging of Alzheimer's Disease Neuropathology," *Society for Neuroscience Abstracts* 24(1-2):1219 (1998) ("Christie") is respectfully traversed.

Gervais relates to the use of amyloid-targeting imaging agents for imaging amyloid plaques *in vivo*. The amyloid-targeting imaging agents include an amyloid targeting moiety linked to a labeling moiety. The targeting moiety localizes the imaging agents to amyloid plaques, and the labeling moiety allows the imaging agents to be visualized by ultrasound imaging, computed tomography imaging, magnetic resonance imaging, nuclear medicine imaging, optical imaging, and elastography. Labeling moieties taught by Gervais for use in optical imaging include fluorescent or colored dyes. There is no suggestion in Gervais of using simultaneous multiphoton excitation, as claimed.

Alfano teaches an imaging system in which images of objects within tissue are enhanced by applying a contrast agent to a sample to be imaged, thereby forming a luminous object. The tissue is illuminated and 2 image signals are recorded. These 2 image signals are subtracted to minimize an image component resulting from the tissue and to enhance the

image component resulting from the luminous object. Alfano also fails to suggest the use of simultaneous multiphoton excitation.

The use of simultaneous multiphoton excitation in accordance with the present invention has a number of very important benefits. In particular, multiphoton excitation has a very high resolution capability, on the order of one micrometer (page 20, lines 26-29 of the present application), and can reach unprecedented depths (page 27, lines 15-18 of the present application). In addition to permitting high resolution imaging of living tissue, multiphoton excitation has the unique advantage of incurring only minimal photodamage or toxicity on the living tissue being imaged (page 25, lines 25-26 of the present application). These unique features of multiphoton excitation imaging make possible the detection and observance of certain Alzheimer's Disease-like lesions that are otherwise undetectable with prior art imaging technologies (page 25, lines 21-25 and page 46, lines 11-12 of the present application). Multiphoton excitation methods of imaging also provide the opportunity to evaluate a relatively large 3-dimensional reconstruction of the cerebral vasculature (page 32, lines 17-19 of the present application). Additionally, multiphoton excitation of fluorophores provides a method of imaging with improved background discrimination and reduces photobleaching of the fluorophores (page 12, line 19 to page 13, line 8 of the present application).

Christie is cited to disclose the use of multiphoton imaging to analyze Alzheimer's Disease neuropathology. As set forth in the Declaration of Watt W. Webb Under 37 CFR § 1.132, which accompanied the Request for Reconsideration mailed September 7, 2004 ("Webb Declaration"), Christie begins by citing a number of advantages if this approach were to be successful ("Webb Declaration") ¶ 7). However, Christie does not provide adequate information regarding how to use multiphoton excitation in imaging Alzheimer's Disease neuropathology (*Id.*). After discussing the advantages of such an approach (if successful), the abstract goes on to report the "first steps towards identification of multiphoton approaches to [Alzheimer's Disease] neuropathology" (*Id.*). The abstract then indicates that a technique has been developed for multiphoton visualization of amyloid deposition with a diffusable amyloid-binding fluorophore (*Id.*). This is stated to be useful in observing both plaques and tangles of Alzheimer's diseased brain (*Id.*). What is missing from Christie, however, is anything approaching sufficient information to carry out this reported work (*Id.*).

Firstly, there is no description of how multiphoton excitation can be used to penetrate into the brain (Webb Declaration ¶ 8). As reported in the present application, it is necessary to provide a window in the skull or to "thin" the skull (*Id.*). If this is not done, multiphoton excitation radiation cannot penetrate the skull and image the brain (*Id.*).

There is also no description of what the actual wavelength of the multiphoton excitation emission is (Webb Declaration ¶ 9). Without this information, it is not possible to successfully utilize such excitation (*Id.*).

Christie also fails to provide power level and pulse durations for the multiphoton excitation (Webb Declaration ¶ 10). If this information is not properly selected, it has been found that multiphoton excitation is ineffective in visualizing Alzheimer's diseased brain (*Id.*).

Another deficiency of Christie is how low energy photons are to be summed (Webb Declaration ¶ 11). Again, if this is not done properly, multiphoton excitation will not be suitable for imaging Alzheimer's Diseased brain (*Id.*).

In view of all of these deficiencies in Christie, those skilled in the art would not, based on Christie, have been able to image Alzheimer's Disease neuropathology using multiphoton excitation (Webb Declaration ¶ 12). The outstanding office action fails to respond fully to these points which are set forth in the September 7, 2004, Request for Reconsideration.

Since Gervais and Alfano fail to teach or suggest the use of simultaneous multiphoton excitation of brain tissue for detection of neurodegenerative diseases and Christie does not provide an enabling disclosure of how to carry out such multiphoton excitation, the rejection of claims 1-34 for obviousness over Gervais in view of Alfano and Christie is improper and should be withdrawn.

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: July 26, 2005

Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

Certificate of Mailing - 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450, on the date below.

7/26/05 | Laura L. Trost
Date | Laura L. Trost